Norrie disease resulting from a gene deletion: clinical features and DNA studies

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SUMMARY We describe a family in which two boys with Norrie disease have a deletion of the DXS7 locus. The deletion does not extend as far distally as the OTC or DXS84 loci. A full clinical description of the patients is given in order to establish the range of manifestations of Norrie disease. There is no evidence of any other X linked disease in our patients.

Norrie disease (NDP, McKusick No 31060) was originally described as X linked blindness.1 It is characterised by early vascular proliferation (pseudoglioma) in both retinas, atrophic irides, corneal clouding, and cataracts, progressing to shrinkage of the globes (phthisis bulbi). The eye findings are well described,2-5 but extraocular abnormalities are less commonly illustrated. Diagnosis is usually made on ophthalmological criteria, but we believe that in many cases the disorder is recognisable on general clinical examination.

Carriers have no visual or auditory signs and until recently counselling was based on pedigree analysis alone. A suggestion of linkage between the NDP locus and the glucose 6 phosphate dehydrogenase locus has not been substantiated. However, in 1985 Gal et al6 reported close linkage between NDP and the polymorphic X chromosomal locus DXS7 defined by the probe L1:28, which lies within or close to band Xpl1.3. This linkage has been confirmed.7,8 In one of the seven families studied by Gal et al7 there was a deletion of the DXS7 locus in an affected boy and several female relatives. A second NDP family with a deletion was reported by de la Chapelle et al,9 who used the deletion for carrier detection and prenatal diagnosis.

We describe a family where two affected boys have a deletion of the DXS7 locus, which we believe is only the third such family reported. In addition to describing the DNA findings, we present detailed clinical descriptions and review published cases. We hope this will help to establish the range of clinical manifestations of the NDP gene.

Case reports

V.1 (FIG 1)
V.1 was the first child born to healthy non-consan-

guineous parents after a normal pregnancy. Deliv-
ery was normal and his birth weight was 2.6 kg at
term. His mother noted that his eyes looked cloudy
on the eighth day of life. After ophthalmic evalua-
tion a diagnosis of primary hyperplastic vitreous was
suggested and his left eye was enucleated at 14
months because of shrinkage, pain, and the possi-
bility of a tumour. Developmental delay was ap-
parent from six months but investigations at that
time did not identify the cause. He was referred to
the genetic clinic at two years nine months and for
the first time the family history of blind distant male
relatives was obtained (fig 1). On examination he
weighed 8.1 kg (<3rd centile), length 80 cm (<3rd
centile), and OFC 44 cm (<3rd centile). There was
a prothetic left eye and the right eye was shrunken
with cataract and corneal clouding. His nasal bridge
was narrow and his ears prominent with unfolded
helices (fig 2). Reflexes were abnormally brisk in his
arms and legs and his tone was increased. He could
not sit, crawl, or chew but could hold a cup.

FIG 1 Pedigree of family.
Auditory brain stem electric response test suggested that his hearing was normal, and an EEG showed no focal abnormalities.

Histological examination of the left eye had shown anterior synechiae, ectropion uveae, a cataractous dislocated lens, and total retinal detachment with proliferation of the pigment epithelium forming a pseudo tumour. There was also mild lymphocytic infiltration and the appearances were thought to be suggestive of intrauterine infection. However, after a clinical diagnosis of NDP was proposed, supported by a possible family history, the microscopical changes were reviewed and considered compatible with this diagnosis.

His progress has been poor. His right eye was enucleated because of pain at eight years. Two seizures occurred but a repeat EEG was normal. At nine years he can sit unsupported but has a postural scoliosis, he feeds himself with a feeder cup and spoon, and he has learnt a little sign language. He shows pleasure at the sound of his mother’s voice and at her touch. He constantly grinds his teeth, thrusts his jaw, chews his fist, and scratches his skin. He is very thin with poor muscle bulk and cold extremities. His facial features are fine and his ears large and prominent. Length is 102 cm (<3rd centile) and OFC 46·6 cm (<3rd centile) (figs 3 and 4). His testes are undescended.

v.2 and v.3
The normal four year old brother and two and a half year old sister of the proband have no visual, auditory, or developmental problems.

v.4
He was born at 38 weeks’ gestation after a normal
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pregnancy; birth weight was 2.98 kg, OFC 35 cm. His physical resemblance to V.1 was noted by his mother and she suspected eye problems within two weeks of birth. Examination under anaesthetic at one month showed that the right anterior chamber was totally flat with increased vascularisation; the left pupil was dilated and unresponsive with a dense retrolental membrane. At that time intraocular pressures were normal and neither eye was small. He made extremely slow progress and by nine months could make a range of sounds and hold an object placed in his hand. He was floppy and had poor head control but did appear to respond to handling by his parents.

When examined at 17 months his weight was only 5.92 kg (<3rd centile) and he was severely wasted (fig 5). He was facially similar to V.1 and dissimilar to V.2 and V.3. His nose was narrow, his malar area flat, and his ears large. The left eye was enophthalmic and there were bilateral cataracts (fig 6). He was microcephalic (OFC 42.5 cm, <3rd centile) and his length was 71 cm (<3rd centile). Audiological examination showed dull tympanic membranes and there was low compliance and low middle ear pressure on impedance audiometry. He was admitted to hospital for nutritional assessment and treatment and his weight did increase a little. Periods of decreased awareness and a series of generalised myoclonic jerks were noted but an EEG was normal. His testes are undescended.

II.3, II.7, III.6, III.7, and III.13
These males were all known to II.2 who reported that they were blind, had sunken eyes, and died between infancy and adolescence. Developmental retardation was a feature. We were unable to contact this branch of the family or the medical staff involved with them.

Results of investigations

DNA extraction from peripheral blood leucocytes, restriction enzyme digestion, Southern blotting, hybridisation, and autoradiography were performed as described. Probes were labelled by hexanucleotide primed synthesis. DNA probes L1-28 and 754 define the loci DXS7 and DXS84 respectively; OTC is an ornithine transcarbamylase cDNA. The affected boys showed a deletion with probe L1-28 (fig 7), but not with OTC or 754.

The hexose monophosphate shunt pathway in peripheral blood leucocytes was examined by measuring the increase in NBT reduction after stimulation with phorbol myristate acetate, and the

![Figure 5](http://jmg.bmj.com/)

**Figure 5** V.4 at 17 months. Note severe wasting and large ears.

![Figure 6](http://jmg.bmj.com/)

**Figure 6** V.4 at 17 months. Note sunken eyes, narrow nasal bridge, and thin upper lip.
increase in the level of enhanced chemoluminescence after stimulation with Zymozan. Results were normal. This excludes any defect similar to chronic granulomatous disease.

Urine amino acid chromatography showed normal results. Serum creatine kinase levels were within the normal ranges for the affected boys and their mother. The platelet count on V.4 was normal, and neither boy had any skin manifestations of Wiskott-Aldrich syndrome. No chromosomal abnormality was visible in cultured lymphocytes from the affected boys and their mother. Electroretinography and fundal examination of the mother did not show any evidence of the carrier state for X linked retinitis pigmentosa.

**Discussion**

Boys with X chromosome deletions sometimes have phenotypes which combine features of several X linked diseases. The discovery of deletions in some but not all NDP patients makes it desirable to distinguish those who may have chromosomal deletions spanning several loci from those with typical NDP. Any additional features seen in patients with deletions would then point to genes located on the X chromosome near to the NDP locus. Thus, it is important to know what features constitute the usual phenotype of Norrie disease. Most reports are in ophthalmological publications and concentrate on the eye findings. There are few full clinical descriptions.

Mental retardation of a moderate or severe degree is present in two-thirds of cases, and further regression is sometimes reported. There are reports of odd manneristic behaviour patterns, not necessarily those associated with other blind subjects, and psychotic behaviour is described in some affected males surviving to adult life. Self mutilation was reported by Warburg in one patient and was noted in our patient V.1. Seizures or abnormal EEGs or both have been frequently reported.

Microcephaly was present in the six patients of Moreira-Filho and Neustein, in the patient of Gal et al., and in our two patients. OFCs are not mentioned in most reports even where there was severe mental retardation, but there was an abnor-
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Norrie disease is characterized by severe mental retardation, motor retardation, and seizures. It is caused by a deletion on the X chromosome. The clinical features include hypotelorism, low weight, and chronic respiratory failure. The deletion affects the DXS7 locus, which is linked to the Norrie disease gene. The deletion can be detected using Southern blots and RFLPs. Immunological studies were carried out by Dr Richard Pumphrey and Probes L1:28 and 754 were a kind gift from Professor Peter Pearson and the OTC probe from Dr Kay Davies. RCM is supported by a Special Medical Development Grant from the UK Department of Health and Social Security.
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References

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